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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,628	09/19/2001	Mihael H. Polymeropoulous	31978-164334	2655

7590 06/01/2004

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EXAMINER	
KAPUST, RACHEL B	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/446,628	POLYMEROPOULOUS ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10,11 and 57-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10,11 and 57-59* is/are rejected.

7)☒ Claim(s) *6 and 60-61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0304*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

Applicant's amendment filed March 12, 2004 is acknowledged. Claim 74 has been canceled. Claims 1-6, 10-11, and 57-61 are pending and under consideration. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections/Objections Withdrawn

The objection to the specification for lacking a priority statement following the title of the invention is withdrawn in response to Applicant's amendment to the specification.

The objection to the specification as lacking sequence identifiers is withdrawn in response to Applicant's amendment to the specification.

The objection to the specification for containing embedded hyperlinks is withdrawn in response to Applicant's amendments to the specification.

The rejection of claims 1-3 and 57-58 under 35 U.S.C. 102(a) as being anticipated by Xia *et al.* is withdrawn because Xia *et al.* do not anticipate a mutated human synuclein protein.

The rejection of claims 10-11 under 35 U.S.C. 103(a) as being unpatentable over Xia *et al.* is withdrawn because Xia *et al.* do not teach a mutated human synuclein protein. Thus it would not have been obvious to one of ordinary skill in the art to engineer a vector or transform a host cell with DNA encoding a mutated human synuclein protein.

Claim Rejections - 35 USC § 112

The rejection of claims 1-4, 10-11, and 57-59 under 35 U.S.C. 112, first paragraph for lack of enablement is maintained for reasons of record on p. 5-6 of the office action of paper no. 1003. Claim 5 is newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated human alpha-synuclein mutated to adenine at position 209, does not reasonably provide enablement for any mutated human alpha-synuclein or homolog

thereof or any other mutation at position 209. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that persons of skill in the art will be able to make and use the nucleic acids by using methods described in the specification and methods generally known in the art. Applicants refer to two articles subsequent to the present disclosure that teach other missense mutations in the alpha-synuclein gene that are associated with Parkinson's disease (see p. 14). Regarding the lack of enablement for other mutations at position 209, Applicants argue that there are only a limited number of possible mutations at position 209 that can be made and used, thus it is easily within the skill of an ordinary artisan and would not require undue experimentation.

Applicant's arguments have been fully considered but have not been found to be persuasive. Although the art cited by Applicants shows that it is possible to make and/or use other mutated alpha-synuclein proteins, the example of two mutations does not nullify the fact that it would require undue experimentation to make and/or use the invention as claimed by Applicants. Applicants teach that a mutation to adenine at position 209 of the alpha-synuclein gene is associated with Parkinson's disease (p. 6), however Applicants have not shown that other mutations at position 209 would also lead to a dysfunctional alpha-synuclein protein. Describing a single mutation is merely an invitation to the public to experiment to find others that may exist. Applicants have not provided any guidance to predict that there would be any other mutations that are involved in Parkinson's disease.

In addition, Applicants are claiming any mutated synuclein protein or any homolog thereof. Applicants state that a homolog "is understood to mean any related gene or protein that is at least 25% homologous to the alpha synuclein gene or protein" (p. 16). The proteins claimed by Applicants may have structures and functions that are different from that of the disclosed synuclein mutant or that of a wild-type synuclein protein. Moreover, the proteins claimed by Applicants may or may not be associated with Parkinson's disease. There is no functional limitation on the encoded protein, thus the mutated human synuclein protein or homolog thereof could be significantly different from that of the claimed invention. Certain positions in the encoded amino acid sequence are critical to the protein's structure/function relationship, whereas other positions may be substituted or deleted without affecting the protein's structure/function

relationship. Although Applicants state that a mutant alpha-synuclein protein is meant to be only those proteins which do not perform their usual or normal physiological roles, and the term "mutant" is not meant to embrace sequence variants which encode proteins which are functionally equivalent to normal synuclein proteins (p. 19), a person of skill in the art would not know whether the protein performs its "usual or normal physiological roles" until the gene is cloned and expressed.

Since detailed information regarding the structural requirements of human synuclein mutants and homologs is lacking, the state of the prior art, the unpredictability of the art, the lack of working examples, the breadth of the claims, and the lack of direction provided by the Applicants, it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

The rejection of claims 1-4, 10-11, and 57-59 under 35 U.S.C. 112, first paragraph for failing to comply with the written description requirement is maintained for reasons of record on p. 6-7 of the office action of paper no. 1003. Claim 5 is newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Regarding the lack of written description for mutations at position 209 other than adenine, Applicants argue that the description provided in the specification is clearly adequate to cover the limited number of variants containing a mutation at position 209. Applicants also argue that the two articles cited by the Applicants demonstrate that other missense mutations in the alpha-synuclein gene can cause Parkinson's disease, thus the claimed invention meets the written description requirements for patentability (see p. 15 of response).

Applicant's arguments have been fully considered but have not been found to be persuasive. The instant disclosure of one mutant human alpha-synuclein does not adequately describe the scope of the claimed genus, which encompasses hundreds of different nucleotide sequences. As discussed above, the genus as disclosed by Applicants encompasses nucleotide sequences that are at least 25% homologous to SEQ ID NO: 1 and alpha-synuclein sequences

wherein the mutation is a substitution, deletion, transversion, or transition. Although other mutations in the alpha-synuclein gene can cause Parkinson's disease, the mutations cited by the Applicants are all subsequent to the filing of the current application. 35 U.S.C. 112 requires that the Applicants had possession of the claimed invention at the time the application was filed. At the time the application was filed, the only mutation known to be associated with Parkinson's disease was that taught by Applicants. At the time of the filing of the application, one skilled in the art would not be able to visualize or recognize the identity of the full scope of nucleotide sequences claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the human alpha-synuclein having a mutation at position 209, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated alpha-synuclein polynucleotides having a mutation at position 209 but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Conclusion

Claims 6 and 60-61 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 1-5, 10-11, and 57-59 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (571) 272-0886. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RBK
5/28/04

JANET ANDRES
PATENT EXAMINER